REMARKS/ARGUMENTS

Claims 47-54 remain pending. As set forth more fully below, reconsideration and withdrawal of the Examiner's rejections of these claims are respectfully requested.

The Examiner has rejected Claims 47-54 under 35 U.S.C. § 112, first paragraph, on the basis that the claimed invention was not described in the specification in such a way as to enable one skilled in the art to make and/or use it without undue experimentation. Applicant respectfully traverses this rejection.

The Examiner states:

> [W]ith regards to enablement . . ., Applicants' data in the specification was [sic] obtained from patients preselected for having multiple sclerosis (active or non-active). Further, Applicants' data are correlative only; no data is presented regarding diagnosis resulting directly from the claimed methods, i.e., wherein the initial diagnosis is not known. Thus, there is no true nexus established between Applicants' data and diagnosis or monitoring of MS.

As described by this statement by the Examiner, Applicants' data have clearly established a correlation between certain biochemical markers and the presence or absence of multiple sclerosis (MS) or active MS. Provided with this established correlation, Applicants submit that one of skill in the art would then be enabled to utilize the markers identified to diagnose and monitor MS. Methods of detecting and monitoring such markers are well known in the art and many of them are described in the specification of the present application. (See, *e.g.,* the specification at page 15, line 8 through page 18, line 12, of the present application.)

In making this rejection, the Examiner makes a distinction between a correlation and a nexus, but this distinction is not understood and the Examiner does not explain why a correlation is unpatentable while a nexus presumably is patentable, or what the distinction is between the two. As the Examiner admits that Applicants' data establish a correlation between certain markers and the presence or absence of MS or active MS, Applicants submit that a "nexus" between the detection of these markers and the presence of MS or active MS has also been established. Applicant is not required to show a perfect or infallible correlation to the degree noted in the rejection. As a general matter, evidence of pharmacological or other biological

activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

In essence, the Examiner's rejection and remarks require Applicants to overcome an enablement standard that would require Applicants to present clinical trial data sufficient to obtain regulatory approval of a diagnostic test for MS. But 35 U.S.C. § 112 does not require that a patent disclosure enable one of ordinary skill in the art to make and use a perfected, commercially viable product. Applicant submits that this standard is inappropriate, as it confuses the standards for patentability with the requirements of FDA approval. FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws, *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) (citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994)), nor is an applicant required to demonstrate that a therapeutic target of a claimed invention is a safe or fully effective diagnostic product for humans. MPEP § 2107.01 and cases cited therein. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be used in human clinical trials. It is improper to request evidence regarding the degree of effectiveness. MPEP § 2107.03 and cases cited therein (emphasis in original). Applicant submits, therefore, that the fact that further testing will be needed to meet the requirements for regulatory approval of a diagnostic test has no bearing on the enablement analysis.

The Examiner cites Bielekova et al. for the proposition that the diagnosis of MS is unpredictable. However, Bielekova et al. does not contain such a teaching. Bielekova et al. is concerned with surrogate endpoints, not with the diagnosis of MS, and all statements made in that reference must be considered in light of establishing surrogate endpoints.

The Examiner also relies on Bielekova et al. for definitions of "biomarker" and

"surrogate endpoint." However, these terms are not used in Applicants' claims. Thus, it is not clear how these definitions are relevant. Moreover, the Examiner seems to be requiring Applicants to establish that their markers are surrogate endpoints. Establishing that a biomarker is a surrogate endpoint requires a much more stringent level of proof than establishing that a biomarker can be used for diagnostic purposes. (See, *e.g.,* Bielevkova et al at the first full paragraph of the text on page 1463, fifth full paragraph of the left column on page 1464, and third full paragraph, left column, page 1476.) It is improper for the Examiner to require Applicants to enable something that they are not claiming, especially when doing so requires a much more stringent level of proof.

Applicants are merely claiming a method that can be used as a tool in the diagnosis and monitoring of MS and active MS. As with almost all diseases, diagnosis and monitoring of MS and active MS will require observing, measuring and monitoring of multiple symptoms and test results. Applicants are only claiming that measurements of the markers that they have identified will be useful as *part* of the information that may be used to diagnose and monitor MS and active MS. This is inherent in the use of the term "comprising" in the claims.

The Examiner relies on Jara et al. as showing that "the invention will be unpredictable with respect to diagnosing MS, since altered levels of the claimed biomarker could indicate a different pathological condition, such as lupus." However, Jara et al. only teach that there are elevated levels of histidine-proline DKP (His-Pro-DKP) found in systemic lupus erythematosis (SLE) patients. Contrary to the Examiner's contention, Jara et al. does not teach anything about the markers recited in the currently pending claims, none of which is His-Pro-DKP. The pending claims recite the measurement of aspartic acid-alanine diketopiperazine (DA-DKP), N-acetyl-alanine-serine diketopiperazine (NAS-DKP) and two compounds of masses 175 and 145. His-Pro-DKP has a mass of 234.25. Accordingly, the measurement of His-Pro-DKP is not covered by the currently pending claims, and the teaching of Jara et al. is not relevant.

The Examiner also relies on Jara et al. as teaching that DKPs are present in a variety of body fluids and tissues. Contrary to the Examiner's contention, Jara et al. only teaches that His-

Pro-DKP is present in serum.

It is further the Examiner's position that those skilled in the art would not know how to detect the markers covered by the pending claims in body fluids other than plasma, serum, cerbrospinal fluid and urine and correlate them to MS or active MS. It is submitted that, to the contrary, those skilled in the art could readily determine how to do this. Such methods are well known in the art and are described in the present application. (See, *e.g.,* page 15, line 8 through page 18, line 12, of the present application.)

For the foregoing reasons, Applicants submit that they have provided an enabling description of the claimed methods of diagnosing and monitoring MS and active MS. Accordingly, Applicants submit that Claims 47-54 are adequately supported by the specification and comply with the requirements of 35 U.S.C. 112, and they request that the Examiner's rejections be withdrawn.

Based on these remarks, Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

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